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Daniel Nathans, Professor and Director, Department of Microbiology, Johns Hopkins University School of Medicine.

I want to thank the members of the Committee for giving me this opportunity to express my views on recombinant DNA research. Before getting to the substance of what I have to say let me identify myself. I am a microbiologist with past training in internal medicine and molecular biology. For the last six years I have been Professor and Director of the Department of Microbiology at the Johns Hopkins University School of Medicine in Baltimore. In addition to teaching medical microbiology, molecular biology, and genetics, I do research on tumor viruses. Recently, one of my students and I have been using recombinant DNAs in our research. My research has been supported by the National Institutes of Health, the American Cancer Society, and the Whitehall Foundation, and my salary is paid by the Johns Hopkins University. I have served on Advisory Committees of the National Institutes of Health, and the American Cancer Society, and I was a member of the National Academy of Sciences Committee on Recombinant DNA that called for a voluntary moratorium on certain recombinant DNA experiments and for the development of research guidelines. I am now a member of the Advisory Committee for the Virus Cancer Program of the National Cancer Institute. The main points I want to make in this testimony are:

1) Recombinant DNA methodology represents a truly major development holding high promise for understanding normal and abnormal life processes of complex organisms including man, and for the solution of certain important medical problems.

2) With some exceptions the potential risk to public health from recombinant DNA research is likely to be very low.

3) The NIH guidelines on recombinant DNA research are a conservative response to those potential risks.

Recombinant DNA technology is an outgrowth of three decades of research in the genetics of microbes. It allows biologists to apply to complex organisms powerful analytical methods of microbial genetics and biochemistry, and also allows them to extend these techniques considerably by adding an ability to synthesize new gene combinations. I won't dwell on the expected benefits of recombinant DNA research, since I have been asked to concentrate primarily on an analysis of risks, but I would like to summarize my views on the biomedical benefits very briefly.

Probably the most far-reaching and the surest biomedical benefit will be the profound insights into the genetic basis of human development and disease. The practical implications of this knowledge we can only barely see. Shorter term, probable benefits are the produc- of human and microbial proteins useful in medical research or in the treatment and prevention of disease. Still other potential benefits, frankly speculative and more distant, include possible new ways to treat or prevent genetic disorders.

Now to the potential hazards of DNA recombinant research. From the very beginning scientists have been concerned about protecting the public from possible harm due to recombinant microbes. How does one assess the hazards of such microbes? We need to begin with

general comments on microbes and microbial pathogenicity. We live in a microbial world. Microbes are all about us, packed within our digestive tracts, on our skin, in the air we breathe, in the food we eat. The earth is populated with a wonderful variety of microbes. Each kind is a specialist and lives where it does because it has adapted to its environment over long periods of time, and thereby outgrows or accommodates to competing microbes. Each has its own turf. That tiny fraction of microbes that cause disease is also made up of extreme specialists. In the course of evolution they have acquired a complex genetic makeup that allows them to overcome the body's defenses in one way or another and in some cases also to spread in populations. When grown artificially in the laboratory, pathogenic microbes commonly lose their disease producing power by mutation. What was once a virulent organism become harmless.

What is the relevance of this to the question of hazards of recombinant research? Well, one of the basic concerns is that when an animal or a plant gene is put into the harmless laboratory strain of E. coli K12 (a bacterium derived several decades ago from human feces and used widely for recombinant studies) that this strain might become pathogenic, and indeed that it might cause serious epidemic disease. In my judgment, and in the judgment of experts in the field of intestinal infections this is a highly unlikely possibility. First of all, E. coli K12 after decades of growth in artificial media has lost its ability to colonize the bowel except under very unusual circumstances as shown by direct feeding tests. Unless conditions are rigged to give it a growth advantage, it doesn't

have a chance against the bacteria already there. Second, the ability of a microbe to cause disease, and particularly epidemic disease, is dependent on having an appropriate set of specialized genes, each of which is needed for pathogenicity. Moreover, the spread of intestinal bacterial pathogens is clearly dependent on poor sanitary measures or improper sewage disposal. It would therefore be very difficult, perhaps not possible, even purposely to turn K12 into some sort of plague bacillus.

There are more subtle hazards that also need to be examined. One of these is based on the demonstrated ability of E. coli K12 to transfer genes to other E. coli strains already in the bowel. Could harmful recombinant genes be spread in this way? Conceivably, yes, and that is why multiply defective K12 strains with very low survival and exceedingly low potential for gene transfer have been developed and why we need to minimize the persistence of recombinant genes in other ways as well. But even were recombinant genes to be transferred in spite of these precautions, unless these genes helped their host bacteria to grow better than their natural competitors, available evidence indicates that such genes are likely to be quickly lost.

Another subtle possible hazard first raised in the "moratorium letter" has to do with the spread of cancer-producing genes either in recombinant bacteria or recombinant viruses. We know there are such genes in many viruses, that almost all of us have been infected with these viruses, and that we generally harbor them in a hidden form throughout our lives. Would similar genes present in weakened E. coli K12 or in recombinant defective viruses be likely to increase

the risk of cancer? We cannot give an experimentally verified answer to this question, but a reasonable judgment is that such defective recombinants would not be as infectious and therefore not as hazardous as the natural pathogenic viruses to which we have already been exposed and to which we continue to be exposed. As I indicate later, the uncertainty in this area is taken into account in the NIH guidelines.

Another type of potential risk discussed with poetic force by Robert Sinsheimer is the long term risk of altering microbial evolution in ways inimicable to ourselves and to our environment. As Sinsheimer put it, "Nature has developed strong barriers against genetic interchange between species. What do we know of the consequences of breaching these barriers? In particular and specifically, what may in time ensue if we introduced genetic intercourse between ourselves ... and the ubiquitous microorganisms with which we live so intimately?" Although I know of no sure answers to this concern, I would point out that the intimacy between microbes and other life forms might already include genetic interchange. Microbes decompose us when we die. They are exposed to the plant and animal foods we eat, and to large numbers of cells shed in our intestinal tracts or on our body surfaces. In certain common diseases bacteria or other microbes persist for years inside human cells. And some cellular organelles are widely thought to have evolved from intracellular bacteria. It therefore seems likely, but by no means certain, that some bacteria regularly take up DNA from animal and plant sources. In the case of viruses, natural recombination with cellular DNA is an established fact. Perhaps experiments can be devised to determine

whether this is so with bacteria also. Another point relevant to Sinsheimer's question is one I discussed earlier, namely, the very low probability that unselected foreign genes will survive in nature, particularly with the kinds of microbes required by recombinant experiments under the NIH guidelines. Therefore, though we cannot know for certain "what may in time ensue," I believe there are substantial arguments aginst expecting the worst.

To sum up my views on biohazards: Up to the present time, and admittedly this is a short time, there is no reason to believe that research with recombinant DNA has led to the emergence of harmful microbes. Based on what is known of natural selection in the microbial world, the mechanisms of pathogenicity and spread of microbes, and the properties of defective microbes used in recombinant DNA research, the probability is very low that recombinants constructed under the NIH guidelines will be capable of survival in the natural world or spread in populations.

Having come to these conclusions, I do not want to leave you with the impression that available evidence excludes the <u>possibility</u> that harmful microbes will emerge from recombinant DNA research. That is not the case. Although I believe this eventuality is unlikely, for the reasons I indicated, clearly one can never disprove possibilities of this sort. Experiments to test survival and pathogenicity of particular recombinants, now being planned, may change our judgments, but they are not likely to resolve many uncertainties. It was just these considerations that led to the original call for a pause in specific recombinant experiments and to the NIH guidelines. Because

of the uncertainty, researchers are required under the guidelines to use levels of physical and biological containment far in excess of what has been common and successful practice for many decades in the safe handling of known pathogenic microorganisms, such as those causing typhoid fever, or diphtheria, or pneumonia. In this sense the guidelines are conservative, providing a margin of safety beyond what is probably needed. Given the uncertainties and the preeminent need to protect the public and those involved in recombinant DNA research, such conservatism is clearly warranted.

Thank you.